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Nitric oxide therapy in COVID-19 patients with acute respiratory distress in intensive care unit

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ABSTRACT

Aims: The administration of inhaled nitric oxide (iNO) is a promising and new approach to treat viral load while increasing oxygenation directly. This research aimed to elucidate the clinical and laboratory response to the treatment of the patients diagnosed with Coronavirus disease-19 (COVID-19) in the intensive care unit (ICU) and followed up due to respiratory failure and given iNO.

Methods: A total of 46 individuals who were diagnosed with COVID-19 and developed severe respiratory failure were followed up with or without intubation, had previously received standard care were evaluated within the study's scope. iNO initiation time in the ICU, whether the patients were intubated, clinical and laboratory parameters before and after iNO treatment were obtained from hospital records.

Results: A statistically significant difference has been achieved in arterial partial pressure of oxygen (PaO_2), peripheral oxygen saturation (SpO_2), and the ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO_2/FiO_2) ratios before and after iNO ($p<0.05$). While significant differences were observed in oxygenation with iNO treatment, no significant differences were observed in other parameters. When iNO onset times were evaluated, it was determined that the initiation time of iNO treatment was significantly later in patients who died. The relationship between the duration of mechanical ventilation, the duration of stay in the ICU, and the onset of iNO was a statistically significant relationship between all measurements ($p<0.05$).

Conclusion: iNO has been suggested as an alternative rescue method before invasive treatment in guidelines, especially for the relief of hypoxemia. However, the effective dose and safety of iNO is still not clear.

Keywords: Nitric oxide, inhaled nitric oxide, COVID-19, acute respiratory distress syndrome, intensive care unit

INTRODUCTION

COVID-19, caused by the SARS-CoV-2 virus, is a worldwide pandemic described clinically as viral pneumonia. While some COVID-19 patients have a mild course, like a cold, many may develop acute respiratory distress syndrome (ARDS), which progresses to more severe lung damage and requires intensive care admission. The coronavirus epidemic; constitutes an international public health emergency. COVID-19 pandemic has caused an intense loss of human life worldwide and presents an extraordinary challenge to public health systems and the world economy. It created an abnormal burden on health workers and was very emotionally worn out.[1]

ARDS is a frightening complication in COVID-19 patients.[2] Unlike ARDS, the main mechanism is due to the ACE-2 receptor. The ACE-2 receptor is the key receptor that binds with the SARS-CoV-2 protein. ACE-2 plays an important role in the progression of ARDS. Binding to the cell surface, SARS-CoV-2 suppresses ACE-2 expression. As a result of the decreased ACE-2 level, the conversion of angiotensin 2 to angiotensin 1 is reduced, and unopposed Angiotensin 2 dominance occurs. Undesirable effects of increased angiotensin 2, such as pulmonary vasoconstriction, increased vascular permeability, pulmonary edema in hypoxic conditions, inflammatory cytokine release in the lung, and increased apoptosis, can be achieved.[3,4]

In the pathogenesis of COVID-associated ARDS or, in other words, CARDS, pro-inflammatory cytokines are first released from monocytes, and pneumocyte apoptosis is induced. Other cytokines are released from monocytes, increasing capillary permeability, and neutrophil migration begins. Alveolo-capillary membrane destruction is

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initiated via neutrophils. As a result, protein-rich interstitial and alveolar edema occurs.[5] Pathophysiologically, this condition resembles the typical ARDS, however, there are some differences between typical ARDS and CARDS. Typical Berlin criteria defined ARDS onset time as 'new or worsening respiratory distress occurring within the first week.6 However, studies have shown that the onset time of ARDS in COVID-19 is later than this period.[7]

In a retrospective study conducted on 191 patients in China, the mean ARDS onset time was reported as approximately day 12.7. CARDS have worse outcomes than ARDS from other causes. The mortality of typical ARDS in the ICU is 35%, and hospital mortality is 40%. However, mortality ranges between 26% to 61.5% in COVID-19 patients admitted to ICU due to ARDS, while the mortality rate in mechanically ventilated patients could vary between 65.7% and 94%.[8] Risk factors for poor outcomes include the presence of comorbidities such as advanced age, hypertension, cardiovascular disease, chronic renal failure, diabetes mellitus, low lymphocyte counts, and high D-dimer levels.[9]

The use of iNO in ARDS has been suggested in the literature. Since iNO does not contribute to survival, its routine use in ARDS is not recommended.[10] However, it can be used in severe respiratory failure that does not respond despite the use of advanced ventilation techniques.[11] It is advised to utilize iNO in cases of severe hypoxemia brought on by CARDS because of its good effect on oxygenation in the literature.[12,13] One study showed that iNO temporarily improved oxygenation and reduced the rate of severe respiratory failure, but did not reduce mortality or length of stay in the ICU or hospital.[14] The aim of this research was to elucidate the clinical and laboratory response to the treatment of the patients who were diagnosed with COVID-19 in the ICU and followed up due to respiratory failure and given iNO.

METHODS

A total of 46 patients hospitalized in the ICU due to ARDS with a confirmed diagnosis of COVID-19 between 01.03.2020 to 01.03.2022 and treated with iNO have been enrolled in this retrospective analysis. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. As this was a retrospective analysis, informed consent was not mandatory from enrolled patients. Informed consent was obtained from all participants. The study was carried out with the permission of Ankara City Hospital No:1 Clinical Researches Ethics Committee (Date: 17.08.2022 Decision No: E1-22-2747).

Individuals diagnosed with COVID-19 and developed severe respiratory failure were followed up with or without intubation and had previously administered treatments according to guidelines were evaluated within the scope of the study. Gender, age, comorbidity, intensive care scores (SOFA, APACHE), and length of stay in the ICU were recorded. After the diagnosis of COVID-19, the onset time of iNO and whether the patients were intubated were obtained from hospital records. The dose of iNO given continuously to intubated and non-intubated patients was 20 ppm. Demographic data were collected together with the treatment regimens. Ferritin, interleukin-6 (IL-6), C-reactive protein (CRP), procalcitonin (PCT), D-dimer, fibrinogen, troponin, urea, creatinine, alanine transaminase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH) on the day before iNO administration and three days after iNO administration, lymphocyte count, neutrophil count, platelet count, lactate, oxygen values (PaO_2, SpO_2, $PaCO_2$, FiO_2/PaO_2) were investigated.

Statistical Analysis

Patient data collected within the scope of the study were analyzed with the IBM Statistical Package for the Social Sciences (SPSS) for Windows 23.0 (IBM Corp., Armonk, NY) package program.

Frequency and percentage were given for categorical data and median, minimum, and maximum descriptive values for continuous data. "Mann Whitney U Test" was used for comparisons between groups, "The Friedman Test" for the comparison of measurement values, "Fisher's Exact Test" for the comparison of categorical variables, and "The Spearman Correlation Analysis" for the evaluation of the relationship between continuous data.

Correlation coefficient (The fact that it is between 0.90 and 1.00 indicates that the relationship between the two variables is very strong.)

- Weak in terms of being between 0.00 - 0.29,
- Between 0.30 and 0.49, the relationship between the two variables is low,
- Between 0.50 and 0.69, the relationship between the two variables is medium,
- Between 0.70 and 0.89, the relationship between the two variables is strong.

The results were considered statistically significant when the p-value was less than 0.05.

RESULTS

Within the scope of the study, 46 patients, 30.4% (n=14) female and 69.6% (n=32) male, were evaluated. The ages of the patients ranged from 20 to 80 years, with a mean age of 55 years (**Table 1**).

Table 1. Distribution of demographic and clinical findings of the patients

Characteristics (n=46)	n (%) or Median (Min - Max)
Age, years	55 (20-80)
Gender	
Female	14 (30.4)
Male	32 (69.6)
BMI (kg/m²)	26,5 (17-35)
Comorbid disease	36 (78.3)
Hypertension	24 (52.2)
DM	16 (34.8)
CAD	3 (6.5)
COPD	5 (10.9)
Malignity	3 (6.5)
Heart failure	4 (8.7)
Immune deficiency	3 (6.5)
Pulmonary emboli	2 (4.3)
Transplantation	4 (8.7)
Renal failure	2 (4.3)
Other	6 (13)
Epilepsy	1 (2.2)
Pregnancy	1 (2.2)
Hyperthyroidism	1 (2.2)
Idiopathic pulmonary fibrosis	1 (2.2)
Obesity	1 (2.2)
Cerebrovascular disease	1 (2.2)
Computerized tomography CORADS	
Low	2 (4.3)
Suspicious	18 (39.1)
High	25 (54.3)
Extremely high	1 (2.2)
Apache - 2 Scores	18 (6-43)
SOFA scores	4 (2-12)
Intubation	44 (95.7)
Day of intubation	5,5 (1-50)
Duration of mechanical ventilation, day	19 (0-89)
Length of ICU stay, days	22.5 (2-97)
Nitric oxide initiation time (when positive), days	16 (3-68)
Nitric oxide initiation time (after ICU entry), days	9.5 (1-57)
Nitric oxide delivery time	3 (1-16)
Vasopressor/inotrope requirement before nitric oxide	12 (26.1)
Need for vasopressor/inotrope after nitric oxide	32 (69.6)
Sepsis before nitric oxide	10 (21.7)
Cytokine filter	14 (30.4)
ECMO	5 (10.9)
ARF	14 (30.4)
Dialysis	9 (19.6)
Mortality	39 (84.8)
Mortality (first month)	22 (47.8)
Cause of death	
Multiple organ failure	2 (5.1)
Septic shock	34 (87.2)
Shortness of breath	3 (7.7)
Tracheostomy	6 (13)
PNX	9 (19.6)

There was at least one comorbid disease in 78.3% (n=36) of the patients. The most common comorbid disease was hypertension with 52.2% (n=24). While the mortality rate of the patients in the first month was 47.8% (n=22), it was determined that the mortality rate was 84.8% (n=39) during the study period (**Table 1**).

The distribution of laboratory parameters of the patients included in the evaluation before iNO, on the first, second and third days after iNO treatment were elaborated in **Table 2**. When the table was examined, it was observed that there was a statistically significant difference in the ratios of PaO_2, SpO_2 and FiO_2/PaO_2, which are laboratory parameters measured before and after iNO ($p<0.05$).

The distribution of the relationship between the duration of mechanical ventilation, the duration of stay in the ICU, and the onset of İno was denoted in **Table 3**. When the table was examined, it was seen that there was a statistically significant relationship between all measurements ($p<0.05$).

Table 3. Distribution of the relationship between mechanical ventilation time, ıntensive care unit stay, and nitric oxide onset time

		Duration of MV	Duration of stay in the ICU	NO initiation time
Duration of MV	Correlation coefficient	1.000	0.855	0.542
	p-value	-	<0.001	<0.001
Duration of stay in the ICU	Correlation coefficient	0.855	1.000	0.655
	p-value	<0.001	-	<0.001
NO initiation time	Correlation coefficient	0.542	0.655	1.000
	p-value	<0.001	<0.001	-

The distribution of the relationship between the intubation status of the patients before or after iNO usage and their final status was given in **Table 4**. When the table was examined, 81.8% (n=18) of the patients intubated before iNO died, while 95.5% (n=21) were intubated after iNO deceased. This relationship between the two groups was not statistically significant ($p<0.05$).

Table 4. Distribution of the relationship between mechanical ventilation time, ıntensive care unit stay, and nitric oxide onset time

		Mortality		p-value
		Survived	Deaceased	
Intubation Time	Before	4 (18.2)	18 (81.8)	0.345
	After	1 (4.5)	21 (95.5)	

Table 2. Distribution of laboratory parameters of the patients before and after nitric oxide

Laboratory Parameters	Before NO	NO (Day 1)	NO (Day 2)	NO (Day 3)	p-value
	Median (Min-Max)	Median (Min-Max)	Median (Min-Max)	Median (Min-Max)	
IL-6	27,2 (4,6-5500)	28.2 (3.1-5500)	22.5 (2.8-5500)	18.9 (2,2-374)	0.362
CRP	0,09 (0,01-0,33)	0.07 (0.01-0.38)	0.08 (0.01-0.21)	0.07 (0.01-0.34)	0.208
Lymphocyte	0,5 (0,1-2,1)	0.5 (0.1-2.4)	0.5 (0.1-3.6)	0.5 (0.1-2.2)	0.241
Ferritin	865,5 (47-11371)	903.5 (66-14278)	805 (47-43078)	750.5 (62-7255)	0.740
Procalcitonin	0,2 (0-23,9)	0.3 (0-229.9)	0.2 (0-40)	0.3 (0-18.9)	0.508
D-Dimer	4 (0,3-36,6)	4.2 (0.5-55)	4 (0.2-35.2)	3.3 (0.3-35.2)	0.806
pO_2	52,4 (47-70)	68.1 (50-101)	71 (50-98)	68.6 (49-87.1)	<0.001
sO_2	80 (66-92)	91 (76-98)	92 (78-98)	91 (73-99)	<0.001
pCO_2	45,2 (22-119)	47 (26.9-284)	48.1 (25-98)	49.3 (29.8-103)	0.979
Ph	7,4 (6,8-7,5)	7.4 (6.9-7.6)	7.4 (7.1-7449)	7.4 (6.9-7.6)	0.975
Laktat	1,7 (0,6-12,1)	2 (0.6-11.8)	1.7 (0.8-12.4)	1.7 (0.8-16.4)	0.546
LDH	567,5 (205-8291)	600.5 (246-8291)	531 (2-3088)	533 (223-3384)	0.850
AST	44,5 (17-9265)	48.5 (16-9265)	46 (14-1321)	49 (14-1828)	0.065
ALT	49 (8-3168)	50 (11-3168)	46 (8-601)	47.5 (12-1577)	0.523
PaO_2/FiO_2	52 (50-71)	75.5 (50-118)	90 (55-120)	79 (50-156)	<0.001

DISCUSSION

In 1987, it was understood that nitric oxide (NO) was the substance known as an "endothelium-derived relaxing factor," which was known to be present in exhaust gas and cigarette smoke and has been positioned as an element of air pollution.[15] NO is a highly lipophilic molecule that can easily cross membranes. As a result of a series of reactions catalyzed by nitric oxide synthesizing enzyme (NOS), L-arginine is converted to L-citrulline, and NO.[16] NOS-II or iNOS is present in the respiratory epithelium and various other cells.[17-19]

The most important finding of ARDS is severe hypoxemia resulting from physiological shunt and ventilation/perfusion (V/Q) imbalance. Inhaled vasodilators such as iNO and prostacyclin increase oxygenation by vasodilation, especially in well-ventilated vessels, and improve V/Q imbalance. iNO is consistently used in the treatment of hypoxic respiratory failure at doses of 1.25-40 ppm.[20] However, in case of interruption or abrupt discontinuation of treatment, it causes serious deterioration in oxygenation and a sudden increase in pulmonary artery pressure. This research found a statistically significant difference in PaO_2, SpO_2, and FiO_2/PaO_2 ratios obtained before and after iNO utilization ($p<0.05$).

The most important features of iNO are selective pulmonary vasodilation, correcting hypoxia, and reducing elevated pulmonary artery pressure by reducing pulmonary vascular resistance. Thanks to its selective vasodilation feature, iNO is a valuable treatment method as a salvage treatment method in all types of pulmonary hypertension and in cases of severe respiratory failure with resistant hypoxia, which is difficult to treat with conventional treatments. Anti-viral drugs currently available to clinicians have little or no effect on mortality, length of hospital stay, need for mechanical ventilation, or long-term effects.[18] In our study, there is not enough data on this subject, since we did not have our patients undergo echocardiography due to pandemic conditions.

The high mortality rates in COVID-19 patients requiring mechanical ventilation are prompting clinicians and scientists to seek new technologies and pharmacological interventions that can improve outcomes. Researchers and clinicians consider iNO therapy promising for patients with COVID-19 and respiratory failure,[21] 13 supported by in vitro research from Akaberi et al.[22] In 2003, during the SARS epidemic in China, a small observational study of patients with SARS pneumonia receiving non-invasive support, biphasic positive airway pressure (BiPAP), were treated with iNO improved oxygenation, accelerated the resolution of chest X-ray infiltrates, reduced the need for intubation, and led to a more rapid and sustained ARDS resolution and improved overall clinical outcomes.[23]

About 30% of patients with severe CARDS in healthcare practice have received iNO as a life-saving therapy.[24,25] However, the results of published randomized trials and clinical observations are highly controversial. Small cohort studies have not significantly improved oxygenation and

clinical outcomes with iNO therapy.[26] On the other hand, the frequency of responders ranges from 25%to 40% with a tendency of a more pronounced effect on gas exchange in patients with right ventricular dysfunction. The percentage of iNO responders is much lower than in patients with non-CARDS.[27] Our observations were that oxygenation improved in patients using iNO.

A retrospective observational study showed that iNO was useful in improving oxygenation in spontaneously breathing patients with COVID-19 pneumonia.[14] High-dose iNO (160 ppm) was safely administered to pregnant women with severe COVID-19 pneumonia and as a rescue therapy to spontaneously breathing patients with COVID-19 and hypoxemic respiratory failure.[28,29] A recent trial of non-invasively treating patients with moderate COVID-19 hypoxia demonstrated that iNO-therapy produced an acute improvement of systemic oxygenation in hypoxemic patients and reduced the respiratory rate.[30] In our study, 20 ppm iNO was used.

Preliminary data support the iNO-mediated improvement of oxygenation in mechanically ventilated patients and spontaneously breathing patients with COVID-19.[31] Another strategy for iNO administration in COVID-19 involves the potential for selective pulmonary vasodilation to optimize V/Q matching by reducing pulmonary vascular resistance and decreasing alveolar dead space. In this research, we found a statistically significant relationship as positively correlated in all parameters when we examined the relationship between the duration of mechanical ventilation, the duration of stay in the ICU, and the onset of iNO. The reason for this relationship is due to the known hypoxemia correction mechanism of iNO and less complications related to hypoxemia.

The study of iNO treatment in spontaneously breathing COVID-19 patients demonstrates not only an increase in oxygenation in all patients, but also provides evidence that iNO therapy may have a role in preventing the progression of hypoxemic respiratory failure.[14] In this study, when the living and deceased patients were examined, it was seen that whether ino was given before and after intubation did not affect mortality in both groups.

iNO has been suggested as an alternative rescue method before invasive treatment, especially for the relief of hypoxemia. However, according to recent clinical trials in Italy, iNO appears unable to reverse oxygenation in patients with extensive mechanical ventilation who have developed persistent hypoxemia.[26,27] Therapeutic doses for COVID-19 patients range from 20 to 300 ppm. Only a few studies have examined the safety and efficacy of 80, 150, and 160 ppm iNO. The results of these studies have yet to be published.[25]

CONCLUSION

iNO can be used as a rescue therapy in patients who develop severe respiratory failure due to COVID-19 and do not respond to all recommended treatments, since it corrects hypoxemia. The therapeutic effects of iNO in COVID-19 and the safe and effective dose for iNO are still unclear. This therapy could pave the way for better management of COVID-19 before the onset of disease-related complications. However, due to the small number of patients in our study, it is not possible to reach a definite conclusion. Due to this situation, which led to the limitation of our study, it should be supported by studies with large sample size.

Abbreviations

ACE: Angiotension converting enzyme, ARDS: Acute Respiratory distress syndrome, ARF: Acute renal failure, BMI: Body mass index, CAD: Coronary artery disease, COPD: Chronic pulmonary obstructive disease, DM: Diabetes mellitus, ECMO: Extracorporeal membrane oxygenation, ICU: Intensive care unit, iNO: Inhaled nitric oxide, LDH: Lactate dehydrogenase, MV: Mechanical ventilation, NO: Nitric oxide, RT-PCR: Real Time polymerase chain reaction, SPSS: Statistical package for the social sciences

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Ankara City Hospital No:1 Clinical Researches Ethics Committee (Date: 17.08.2022 Decision No: E1-22-2747).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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